Desired and undesired effects of antipsychotic treatment from a patients' perspective

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Chapter 6

General discussion

Experiences of the mentally ill.

Warmark, an early twentieth-century British psychiatric patient, remarked in his autobiography: “One half of mankind does not know how the other half lives” (Peterson, 1982). For a long time psychiatric patients were generally treated as if their experiences were unimportant. For example, John Perceval (1838) accused the staff of treating him “as if I were a piece of furniture, an image of wood, incapable of desire or will as well as judgement”. Since the conceptualization of schizophrenia as a neurobiological disease, some experts have declared that it is unnecessary to communicate with schizophrenic patients. To quote Hunter and Macalpine (1974) “Patients are victims of their brain rather than their mind. To reap the rewards of this medical approach, however, means a reorientation of psychiatry, from listening to looking.” This approach is more or less still prevalent in, for example, the financial-administrative procedures of the Diagnosis Treatment Combination (DBC) and in the treatment guidelines in the Netherlands: if you know what is wrong, you know the treatment. Since the introduction of the first antipsychotic medications, the medicalization of psychiatry has been reinforced. Why would we take patient’s opinions, experiences, and responses into account if it is widely agreed that schizophrenia is a neurobiological disease?

Although, it is commonly accepted that antipsychotic medication is a necessary component in the treatment of psychotic symptoms, or even the cornerstone of treatment, and that it has been proven to be effective, non-compliance is a great problem. The majority of schizophrenia patients decide to discontinue therapy due to perceived inefficacy, intolerable side effects, or for other reasons (Lieberman et al., 2005). Low adherence rates are associated with worse physical and mental health outcomes (Marder, 1998; Moore et al., 2000). This underscores the point that patients’ preferences, experiences, and opinions are important factors in optimizing outcomes. The shift from a doctor’s perspective to a more client-centered approach is also present in the definition of evidence-based medicine, which includes patients’ preferences, along with scientific evidence and clinician’s skills, as a pillar of medical decision making (Sackett, 1997). The focus on the patient is also seen in the implementation of the shared decision-making model (Drake et al., 2009) where the health care professional and the patient have their own areas of expertise and negotiate and

commit to a collaborative agreement. The recovery movement also focuses more on the personalized context and collaborative management of a treatment (Amering, 2009). The Subjects' Response to Antipsychotics Questionnaire fits in these client-centered approaches. However, during the development of this instrument several issues were raised.

Conceptual issues

Subjective versus objective treatment effects, what's in a name?

Some experiences with antipsychotic medication are difficult for clinicians and researchers to evaluate and instantiate. These are described in terms like "behavioural toxicity" (DiMascio, 1970), "dysphoric response" (Van Putten and May, 1978a) , "subjective response" (Singh, 1976;) and "subjective well-being" (Naber et al., 1998) (see Chapter 1). In research and clinical practice the preferred term for these types of experiences is 'subjective treatment effects'. At the onset of this study we started with Subjective Response to Antipsychotics as a name for the scale. However, the word 'subjective' implies a contrast with objective. 'Subjective' may suggest that it only relates to experiences which are unobservable by a third party, and it may also imply a negative connotation, doubts as to whether they are real or accurate. In an attempt to emphasize a more descriptive and fundamental position in taking the opinion of the patient as primary and central, the term subjective was abandoned. Leaving the acronym unchanged, the questionnaire was renamed the Subjects' Response to Antipsychotics (SRA) questionnaire. Research, to date, has supported this choice, showing that many of these 'subjective' effects correlate strongly with pharmacological properties of antipsychotics, especially their influence on the dopamine system (e.g. De Haan et al 2005).

The decision to include attribution in the wording of the items

Adding the attribution of the experiences to the antipsychotic medication in the wording of the items was a point of debate in the development of the final version of the questionnaire. Naber (1994) stated that patients, as well as clinicians, are unable to distinguish between medication-related and disease-related components. For instance 'affective flattening' may be a symptom originating from the pharmacological blockade of dopamine, but may also arise from depressive or negative symptoms. Although attribution of experiences by patients may in some instances be incorrect it will still influence the patient's evaluation of the

treatment and, therefore, probably influence his adherence. This makes the experience and its attribution clinically relevant. So although patients may be wrong in attributing symptoms to antipsychotics, omitting attribution in the questionnaire may lead to other sources of bias and restrict the applications of the questionnaire. To test whether the decision to maintain the attribution aspect was justifiable, we examined whether the SRA scales reflect pharmacological effects. Chapter 3 shows that several scales correspond with the well-known pharmacological effects of the studied antipsychotic medication, supporting the view that most patients report experiences to antipsychotics in a consistent and pharmacologically rational way.

Side-effects versus subjects' responses

Another conceptual question is the difference between side-effects and subjects' responses. Side-effects are defined as more or less unavoidable, at least in a certain proportion of treated patients, dose-related undesired consequences of the (well-known) pharmacological effects of the drug (Lingjaerde et al., 1986). According to this definition, effects like weight gain and sedation are side-effects. However, from a pharmacological perspective there are no 'side-effects', but only effects of a drug on an organism. Some of them may be desired and are often summarized in terms of efficacy of a drug. Other effects may be undesired, and are referred to as the tolerability, or side-effects, of a drug. The goal of treatment and the interpretation of its effect by the observer (e.g. patient, doctor or family) determine whether an effect is labeled desirable or undesirable. To avoid the negative connotation of side-effect we used the terms desired and undesired responses, as evaluated by the patient.

The questionnaire

Systematic evaluation of treatment effects with rating scales is preferable to informally interviewing the patient during a consultation. A rating scale allows for comparisons between different moments (e.g. after a medication change) and patients (e.g. for research). A self-rating scale is also time-efficient, because patients can fill in the questionnaire at their convenience.

When developing a scale measuring patient's responses to antipsychotics it is important to select relevant experiences that are meaningful to the patient. The composition of items in existing instruments, like the Drugs Attitude Inventory (DAI; Hogan et al., 19) and the

Subjective Well-being on Neuroleptics (SWN; Naber, 1998), was based on clinical expertise and extant scientific literature. Although this may be an efficient way to develop a questionnaire, it remains unclear if these items indeed reflect the experiences and views of the patients. One of the strengths of the SRA-questionnaire is the bottom-up strategy of interviewing patients to inform item development. This approach also has the advantage of adhering to the wording of the patient as closely as possible. The details of the item construction and selection processes are described in chapter 2.
At first these items were categorized in several domains with a positive-negative evaluation dimension and a decrease-increase dimension. During the psychometric evaluation, several drawbacks of these categorizations were found. The clinical utility is hampered because of the complexity of the scoring procedure. Also, the clinical relevance of these categorizations was questionable. To make a more useful categorization, clinical experts were asked to construct a priori scales. The drawback of this approach is the loss of items tapping patient evaluation of experiences like sedation and sleep, which some evaluate as desired and some as undesired. However, the psychometric evaluation of the instrument supported the categorization made by experts.

We tried to make the scale as comprehensive as possible. However, the chosen method to develop the SRA using a bottom-up approach may have led to an underestimation of undesired treatment effects, both quantitatively and qualitatively, as patients who discontinued antipsychotic medication were not included in the sample used to construct the items and are not represented in the validation studies. Although patients using first and second generation antipsychotics were interviewed, no patients using the newest generation of antipsychotics like aripiprazole were part of the interview study, because these drugs were not yet on the Dutch market at the time of the study. This may have influenced the item set and possibly led to missing or underestimating some treatment effects. An open question asking about effects that were not included in the instrument was placed as the last item on the questionnaire to partly address this problem.
In the original questionnaire the miscellaneous items were not deleted, because these items may be clinically relevant. Although the patient perspective was central in the development of the SRA, and, therefore, all items were retained in the final version, it may be argued that the SRA can be shortened by deleting the miscellaneous items without losing essential

information. It takes about 20 minutes to fill in the complete questionnaire, which may be too long for use in, for example, Routine Outcome Monitoring (ROM). For research and ROM, the short form without the miscellaneous items is probably preferable.

Overall, the questionnaire appears to be valid and reliable. However, in the psychometric process some issues concerning reliability and validity were raised in the sexual function and sedation domains. The problems with test-retest reliability and validity in the sexual function domain are not restricted to the SRA, but are also found in other studies of other measures (e.g. Knegtering, 2003). A possible explanation is the rather narrow time frame, one week, patients are asked about their responses. Also, these findings could reflect limitations of the bottom-up strategy for item construction, as sexuality is a sensitive topic for many patients. Not all known dimensions of sexual function (e.g. desire, arousal, orgasm and ejaculation) are represented in the item set of the SRA.
One explanation for why the sedation subscale did not correspond with known sedative antipsychotics may be that the items in this subscale reflect a lack of mental and physical energy, which is a broader concept than sedation. In fact, the term 'sedation', as used in most pharmacological research, often does not differentiate between hypno-sedation, flattening of affect, or lowering of energy levels. The term 'sedation' may not distinguish between pharmacologically distinct properties like antihistaminic effects (inducing sleepiness or drowsiness) or antidopaminergic effects (diminished initiative and flattening of affect). The questionnaire may encompass more details than the validation method allowed for.

Comparison of questionnaires
We identified three other relevant self-rating instruments in a literature search (year 2000) for the evaluation of subjective side-effects of antipsychotic medication: the Drug Attitude Inventory (DAI-10; Hogan et al., 1983), the Liverpool University Neuroleptic Side Effect Rating Scale (LUNSERS; Day et al., 1995) and Subjective Well-being under Neuroleptics (SWN; Naber, 1994).
There are significant differences between these instruments, for more detail see chapter 5. The LUNSERS measures effects known to be related to the use of antipsychotic treatment. However, this instrument measures not the whole spectrum of effects, but only side-effects.

Also, ratings on the LUNSERS do not imply a relation between the complaints and the treatment. The SWN measures treatment effects, but also encompasses other sources of malaise and discomfort. These experiences will usually be attributed to a specific cause. Some will be attributed to the treatment and will be evaluated as desired or undesired. These are the experiences that are measured by the SRA. The balance between desired and undesired effects influences attitudes toward the treatment. This is the focus of the DAI. As such, the type of information that is needed determines which instrument is preferable.

Future research

An important research topic to be explored further is the validation of the SRA with instruments scored by trained experts. It would be of interest to examine whether the subscale "Recovery" correlates with other efficacy measures like improvement on the Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987). This may be helpful in validating the use of the SRA in the efficacy domain. It would be also interesting to examine whether self-reported undesired treatment effects correspond with observed side-effects (for example with the UKU (Lingjaerde et al., 1987).
It is important to tailor antipsychotic treatment to the individual needs of the patient. One of the factors involved in drug treatment compliance is patient satisfaction with the medication. To further validate the SRA questionnaire, the relation with compliance should be examined. The sensitivity of the questionnaire should be tested, for instance, by changing the antipsychotic medication or altering the dose. The questionnaire has been translated in several languages: English, French, Turkish, Arabic and German. For further use in international research the reliability of these translations should be established.

De Haan et al. (1995) found that undesired subjective experiences are related to D2 receptor occupancy by antipsychotics. The subjective experiences were measured by the SWN. It would be interesting to study which SRA domains also show an association with D2 receptor occupancy. If such a relation is found, the SRA could be of help to find optimal D2 receptor occupancy.

Two slightly altered versions of the SRA are under development and being studied. One version is using all original items of the SRA, but groups them in subscales and not at random order as used in this thesis. This may be an advantage in clinical practice, because after completing the questionnaire in a paper and pencil version of the SRA a clinician can immediately see what the clinically relevant issues are. Also, the item set for sexual functioning is being reviewed in order to obtain a more complete set reflecting all dimensions of sexual function. A validation study is underway to examine the validity of this extended subscale.

The SRA may be useful in compliance, effectiveness and pharmacogenetic research. It has been translated in several languages and has already found its way to universities, routine outcome research, clinical practice and pharmaceutical companies. We hope the SRA may be helpful in finding better treatments for our patients.

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